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November 8, 2000

BY HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
12420 Parklawn Drive (HFA-305)
Room 1-23
Rockville, Maryland 20857

Re: Docket No. 96G-0324; GRAS Affirmation Petition for β-Cyclodextrin

Dear Sir\Madam:

On October 7, 1997, we submitted, on behalf of Cerestar USA, Inc. ("Cerestar," formerly American Maize Products Co.), the enclosed opinion by qualified food safety experts (the "Expert Panel") confirming that under the conditions of intended use in foods, Cerestar's β-cyclodextrin (BCD) is "generally recognized as safe" ("GRAS") based on scientific procedures.

It has come to our attention that there was an inconsistency in the exposure estimates relied upon by the Expert Panel in 1997. Specifically, the estimated daily intake (EDI) described in the pending GRAS petition was based on a maximum use level of 2% BCD, whereas the actual food intake survey calculations were based on an expected use level of 0.5%. Upon discovering this discrepancy, the Expert Panel promptly re-evaluated the safety of Cerestar's BCD using the corrected intake calculations based on the 2% use level. Enclosed for your file is the "Amended Expert Panel Opinion of the GRAS Status of Beta-Cyclodextrin (BCD)" which was completed on August 29, 2000 by the Panel.

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Applying the adjusted EDI, the Expert Panel again concluded that Cerestar's BCD, meeting appropriate food grade specifications and used in conformity with current good manufacturing practice, is GRAS based on scientific procedures for its intended use as a flavor carrier/protectant at levels of up to 2% BCD in baked goods prepared from dry mixes; breakfast cereals; chewing gum; gelatins and puddings; dry mixes for soups; flavored coffee and tea; compressed candies (as tablets); processed cheese products; flavored savory snacks and crackers; and dry mix beverages.

Should you have any questions regarding the Amended Expert Panel Opinion confirming the GRAS status of Cerestar's BCD, please do not hesitate to contact us.

Sincerely,

Diane B. McColl

Diane B. McColl
Counsel to Cerestar USA, Inc.

DBM/dmb
Enclosure

cc: Joseph F. Borzelleca, Ph.D.
George A. Burdock, Ph.D.
W. Gary Flamm, Ph.D.

Mike Fuelling, Esq.
Frances Turnak
Cerestar USA, Inc.

Amended Expert Panel Opinion of the GRAS Status of Beta-Cyclodextrin (BCD)

In the autumn of 1997, the attached GRAS opinion statement was drafted and signed by Drs. Joseph F. Borzelleca, George A. Burdock and W. Gary Flamm. This statement addresses the use of BCD in ten food categories for use as a flavor carrier and protectant. The statement needs to be corrected to reflect accurately the estimated daily intake (EDI) to BCD by the upper 90th percentile consumers of the ten food categories. The need for this amendment resulted from an incorrect assumption that the EDI, given in the GRAS affirmation petition filed with FDA (6G0421), was based on a *maximum* use level of 2% BCD for the ten food categories as given below:

FOOD CATEGORY	**Max. Level (% by weight)**
Baked goods prepared from dry mixes	2
Breakfast cereal	2
Chewing gum	2
Gelatins and puddings	1
Dry mix for soup	0.2
Flavored coffee & tea	1
Compressed candy as tablets	2
Processed cheese products	1
Favored savory snackes and crackers	0.5
Dry mix beverages	1

Instead, the EDI was based on *expected* use levels (concentrations) up to 0.5% BCD in these food categories. As the petition (6G0421) seeks approval for use levels of BCD in food up to a maximum of 2%, not 0.5%, the Expert Panel has reconsidered the safety of such use levels for the purpose of this amendment and to correct the record accordingly.

Calculations, presented in the petition (6G0421), based on *expected* BCD use levels of up to 0.5%, combined with food intake survey data conducted by the Market Research Corporation of America (MRCA), resulted in an estimated exposure to BCD of 1.44 mg/kg body weight/day for the 90th percentile consumer. This estimate includes an adjustment for the fraction (or percent) of flavors in these ten food categories that currently use approved flavor protectants (microencapsulation) as described under 21 CFR §172.230, but assumed a total replacement of these protectants by BCD. As there are several such substances under FDA's food additive regulation (21 CFR §172.230) which have been used historically as flavor protectants, the above exposure estimate for BCD is unrealistic and will overstate actual exposure. Furthermore, as the use of flavor protectants has been declining significantly according to Lucas et al., 1999 (Flavor and Extract Manufacturers' Association of the United States 1995 poundage and technical effects update survey. FEMA, Washington, D.C.), there is additional assurance exposure to BCD from its proposed, intended use will not reach or exceed the exposure estimate as based on total replacement of all currently used protectants. In view of these considerations, a 50% replacement of existing flavor protectants is considered adequately conservative. Adjusting the estimate accordingly reduces the exposure

estimate to 0.72 mg/kg body weight/day. However, because the use level is up to a *maximum* of 2%, this estimate must be corrected. As the *maximum* level for each food category is about 4-fold higher on average than the level on which the estimate is based, the estimate of 0.72 mg/kg is multiplied by 4 raising the estimated exposure to BCD by the 90th percentile consumer to 2.88 mg/kg body weight/day.

As the estimated exposure is less than the ADI (acceptable daily intake) of 5 mg/kg body weight/day granted by the Joint WHO/FAO Expert Committee on Food Additives (JECFA) with which the Expert Panel concurs, the Panel concludes that BCD, meeting appropriate food grade specifications, is generally recognized as safe (GRAS) by scientific procedures for its intended use as a flavor carrier/protectant for the ten food categories identified in the original GRAS statement at levels up to 2% when used in conformity with current good manufacturing practice as described at 21 CFR §182.1(b).

Joseph F. Borzelleca, Ph.D., F.A.T.S. — 29 August 2000
Date

George A. Burdock, Ph.D., D.A.B.T. — 23 Aug 00
Date

W. Gary Flamm, Ph.D., F.A.C.T., F.A.T.S. — 8/23/00
Date

EXPERT PANEL OPINION OF THE GRAS STATUS OF BETA CYCLODEXTRIN

The undersigned individuals were asked by Cerestar USA, Inc. (Cerestar) to review available relevant information on the safety of beta-cyclodextrin (BCD) for the purpose of determining whether certain specified uses of BCD in human foods would be generally recognized as safe (GRAS). As evidenced by the attached CV's the undersigned, Joseph F. Borzelleca, Ph.D., George A. Burdock, Ph.D., and W. Gary Flamm, Ph.D. (collectively the "Panel"), are well-established food safety experts, qualified by training and many years of relevant national and international experience in evaluating the safety of food ingredients.

Cerestar provided information on the safety, intended use and estimated consumer exposure to BCD, which was independently reviewed by Panel members. Publicly available data and information in the pending GRAS affirmation petition (6G0421) for BCD were made available to the Panel. In addition, the Panel, in coming to its conclusion concerning the GRAS status of BCD, relied on a search of the scientific literature, other relevant information and their respective years of professional experience addressing related matters. Traditional safety studies with BCD, conducted in accordance with FDA guidelines (FDA, 1982), have been published in the scientific literature and include: chronic (52-week) rat and dog studies; carcinogenicity studies in the rat and mouse; multigeneration studies with a teratology phase in the rat and extensive genotoxicity studies. Following independent review and consideration of the above data and information, a teleconference was held to discuss and review the findings with all Panel members.

BCD is a cyclic heptamer composed of seven glucose units joined by α-1,4 bond linkages. It is produced by the action of the enzyme, cyclodextrin glucosyl transferase, on hydrolyzed starch syrup. The enzyme is obtained from non-pathogenic and non-toxigenic strains of *Bacillus macerans*, *B. circulans* or related strains of *Bacillus*. BCD has the ability to form inclusion compounds with a range of molecules, generally of molecular mass of less than 250. It may serve as a carrier and protectant of food flavors by molecular inclusion.

The Joint Expert Committee on Food Additives (JECFA) of the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) has reviewed BCD at its forty-first and forty-fourth meetings. At the latter meeting, an acceptable daily intake (ADI) of 0-5 mg/kg bw was established based on a no effect level (NOEL) of 1.25% in the diet (equal to 470 mg/kg bw/day) in the 1-year study in dogs and a safety factor of 100. The Scientific Committee for Foods (SCF) of the European Union has also assigned BCD an ADI of 5 mg/kg bw/day.

In the report of the forty-fourth meeting (WHO, IPCS, 1996), the comment was made that, in the mouse carcinogenicity study, one male mouse in the 75 mg/kg bw group exhibited an inflammatory lesion of the lower gastrointestinal tract that was considered a possible cause of death. On the basis of this finding, the monograph suggested that the next lowest dose, 25 mg/kg bw, as the NOEL. However, these data were not used by JECFA to establish the ADI as the Committee considered the lesion to represent a species-specific reaction that was not relevant to setting an ADI. We agree, and have further found from our review of individual animal data and group mean values that no inflammatory lesions of the lower gastrointestinal tract were observed at doses above (225 and 675 mg/kg bw/day) or below 75 mg/kg bw in either the males or females. Based on this review and the above findings, the Panel believes that the inflammatory change found in the one male mouse cannot be regarded a treatment related effect. Accordingly, the above effect in the mouse, as JECFA and the SCF have concluded, should not be used to set an ADI. The Panel agrees with the decision of the JECFA and the SCF to consider the ADI for BCD to be 5 mg/kg bw/day as indicated above.

The uses intended for BCD are as a flavor carrier and protectant at 2% in the following foods: (1) chewing gum; (2) gelatin and puddings; (3) soups prepared from dry mixes; (4) coffee and tea products with added flavors; (5) compressed candies; (6) processed cheese products; (7) savory snacks-crackers with added flavorings; (8) baked goods prepared from dry mixes; (9) beverages prepared from dry mixes; (10) breakfast cereals. The above intended uses would collectively amount to 11 to 15 mg/kg bw/day for the upper 90th percentile consumer (eaters only) assuming all flavors used for the above food categories used carriers/protectants. This determination was made and supported by the petitioners in the pending GRAS affirmation petition using survey data gathered by the Market Research Corporation of America (MRCA). However, because only 14% of the flavors used in the

above foods are encapsulated (use protectants) according to the petitioners' calculations, estimated intake of BCD in these foods must be adjusted accordingly. Assuming BCD were to replace all encapsulating agents/protectants (see 21 CFR 172.230), the estimated amount consumed by the 90th percentile consumer (eaters only) would need to be multiplied by 14%. Hence, the estimated exposure to BCD from all of the above food categories for the 90th percentile consumer (eaters only) would be about 2 mg/kg bw/day, well below the JECFA and SCF ADI.

In conclusion, the Panel finds that BCD, meeting appropriate food grade specifications, is generally recognized as safe (GRAS) by scientific procedures for its intended use as a flavor carrier/protectant for the 10-food categories listed above when used in accordance with current good manufacturing practice as described at 21 CFR 182.1(b).

Joseph F. Borzelleca 01 Oct 1997

Joseph F. Borzelleca, Ph.D., F.A.T.S. Date

George A. Burdock 28 Sept 97

George A. Burdock, Ph.D., D.A.B.T. Date

9/26/97

W. Gary Flamm, Ph.D., F.A.C.T. Date